171

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/989,687	11/21/2001	Luisa Irucla-Arispe	1488.107000D/EKS/CML	9708

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EXAMINER	
CANELLA, KAREN A	
ART UNIT	**PAPER NUMBER**
1642	

DATE MAILED: 05/20/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/989,687	IRUELA-ARISPE ET AL.	
	Examiner	Art Unit	
	Karen A Canella	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☐ Claim(s) *1-8* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) *1-8* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *10/18/2002*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Acknowledgement is made of applicants election of the species of METH2 without traverse.

Claims 5-8 have been added. Claims 1-8 are pending and examined on the merits.
Claims 1-4 are examined to the extent that they read on METH2.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 4 and 8 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 4 and 8 recite "gene therapy means". This term does not provide an active method step to further limit the subject matter of claims 1 and 5, respectively. It is unclear if "gene therapy means" reads on ex vivo transfection of genes into cells and the administration of the resulting transformed cells, or if "gene therapy means" is intended to be the administration of the gene directly to the host by naked DNA injection, or viral vector, etc.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-8 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of treatment comprising the administration of a protein or peptide, does not reasonably provide enablement for a method of treatment comprising gene therapy. The specification does not enable any person skilled in the art to which it pertains, or

with which it is most nearly connected, to make and use the invention commensurate in scope with these claims..

Claims 1 and 5 are drawn to a method of treating an individual comprising administering an effective amount of METH2 wherein said method is used to treat benign tumors, ocular antigenic diseases, vasculogenesis, granulations, hypertrophic scarring, non-union fractures, scleroderma, trachoma, vascular adhesion, myocardial angiogenesis, coronary collaterals, cerebral collaterals, arteriovenous malformations, ischemic limb angiogenesis, Osler-Webber syndrome, plaque neovascularization, hemophiliac joints, angiofibroma, fibromuscular dysplasia, wound granulation or atherosclerosis. Claims 2 and 6 are drawn to a method for treating an individual comprising administering an effective amount of METH2 wherein said method is used as birth control. Claims 3 and 7 embody the method f claims 1 and 5, respectively, further comprising administering another angiogenic compound. Claims 4 and 8 embody the methods of claims 1 and 5 respectively, wherein said METH2 is administered by gene therapy means wherein cells have been modified to produce and secrete METH2. Thus, it is reasonable to conclude that claims 1-3 and 5-7 include methods of administering METH2 by gene therapy means. the instant specification is not enabled for administration via gene therapy means for the reasons set froth below:

The instant specification does not teach how to overcome problems with in vivo delivery and expression with respect to the administration of the claimed nucleic acids or viral vectors comprising said nucleic acids. The state of the art is that in vivo gene delivery is not well developed and is highly unpredictable. For instance Verma et al (Nature, 1997, Vol. 389, pp. 239-242, cited in Paper No. 10) teach that the Achilles heel of gene therapy is gene delivery. Verma et al state that the ongoing problem is the inability to deliver genes efficiently and to obtain sustained expression (page 239, column 3). Eck et al (Gene-Based Therapy, In: The Pharmacological Basis of Therapeutics, Goodman and Gilman, Ed.s, 1996, pp. 77-101, cited Paper No. 10) teach that the fate of the DNA vector itself with regard to the volume of distribution, rate of clearance into tissues etc., the in vivo consequences of altered gene expression and protein function, the fraction of vector taken up by the target cell population, the trafficking of the genetic material within cellular organelles, the rate of degradation of the DNA the level of mRNA produced, the stability of the mRNA produced in vivo, the amount and

stability of the protein produced and the proteins compartmentalization or secretory fate within the cell are primary considerations regarding effective therapy. Eck et al state that these factors differ dramatically on the vector used, the protein being produced, and the disease being treated (Eck et al bridging pages 81-82).

As of the priority date sought, it was well known in the art how to infect or transfect cells in vitro or ex vivo with viral vectors. However, using viral vectors to deliver DNA to an organism in vivo, or using infected or transfected cells to deliver nucleic acids which encode a particular protein sequence to an organism in vivo is in the realm of gene therapy, and as of the priority date sought, highly unpredictable in view of the complexity of in vivo systems. Orkin et al state ("Report and Recommendation of the Panel to Assess the NIH Investment in Research on Gene Therapy", NIH, 1995, cited in Paper No. 10) that clinical efficacy had not been definitively demonstrated with any gene therapy protocol (page 1, second paragraph). Orkin et al defines gene therapy as the transfer of DNA into recipient cells either ex vivo or in vivo (page 7, under the heading "Gene transfer") thus encompassing the instant claims 4 and 8 drawn to the modification of cells to produce and secrete METH2. Orkin et al concludes that, "none of the available vector systems is entirely satisfactory, and many f the perceived advantages of vector systems have not been experimentally validated. Until progress is made in thee areas, slow and erratic success in applying gene transfer methods to patients can be expected" Orkin et al comment that direct administration of DNA or DNA in liposomes is not well developed and hindered by the low efficiency of gene transfer (page 8, paragraph 5). Orkin et al teach that adequate expression of the transferred genes is essential for therapy, but that current data regarding the level and consistency of expression of transferred genes in animal models was unknown. Orkin et al states that in protocols not involving ex vivo infections/transfection, it is necessary to target the expression of the transferred genes to the appropriate tissue or cell type by means of regulatory sequences in gene transfer vectors. The specification does not teach a vector having a specific regulatory sequence which would direct the expression of the nucleic acids within the appropriate tissue type.

The specification does not remedy any of the deficiencies or the prior art with regard to gene therapy. Given the lack of any guidance from the specification on any of the above issues pointed out by Verma or Eck or Orkin. One of skill in the art would be subject to undue

experimentation without reasonable expectation of success in order to practice the methods of claims.

Claims 1-8 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. .

Claims 1-8 are method claims reliant upon the identity of METH2. The specification states on page 111, line 30 that SEQ ID NO:4 refers to "a" METH2 polypeptide sequence. Thus, the recitation of "METH2" in the instant claims is not limited to a single polypeptide of SEQ ID NO:4. The specification states on page 127, lines 1-8 that the invention encompasses METH2 polypeptide which are differentially modified during or after translation, including proteolytic cleavage, derivitization with known protecting/blocking groups, linkage to a cellular ligand. The specification states on page 136, lines 17-20 that the invention includes variants of the METH2 polypeptide which show substantially METH2 polypeptide activity, or proteins comprising regions of the METH2 polypeptide.

The specification states that the invention related to variants of the nucleic acid molecules of the invention which encode portions, analogs or derivates of the METH2 protein , and that variants include allelic variants which occur in nature and which can be produced by mutagenesis techniques (page 101, lines 3-6, page 113, lines 3-9). Thus, when given the broadest reasonable interpretation, the term METH2 encompasses variants, mutants, proteins comprising a fragment of METH2 and chemical modifications of all of the aforesaid embodiments. the specification sets forth SEQ ID NO:4 as a specific embodiment of METH2. The specification sets forth N-terminal deletion mutants of METH2 on page 241, line 29 to page 247, line 15 which include deletion of every residue from 1-885 of SEQ ID N:4, leaving the fragment of residues 885-890 as the smallest fragment contemplated. Likewise the specification sets froth C-terminal deletion mutant of METH2 which range from 1-1889 starting on page 247, line 16 and range to residues 1-7 of SEQ ID NO:4 as the smallest fragment claimed. Thus fragments as small as 8 amino acids are encompassed within the term METH2 as the invention

is contemplated as proteins comprising a fragment of METH2. The specification recites conservative amino acid substitutions of METH2 by listing, for every amino acid positions, all possible conservative amino acids (page 173, line 4 to page 205, line 10). The specification further states that METH2 polypeptides may contain up to 50 conservative or non-conservative amino acid substitutions and that the substitutions may be made in full-length or any other METH2 variant, including N and/or C-terminal deletion mutants, METH2 polypeptides lacking one or more domains or hybrid METH2 molecules (page 205, lines 11-4 and lines 22-26). The specification states that properties of METH2 which may be altered by conservative or non-conservative substitutions include but are nor limited to stimulation of angiogenesis, stimulation of epithelial cell proliferation, antibody binding, ligand binding, stability, solubility and or properties which affect purification (page 214, lines 5-9). The genus of proteins as nucleic acids encoding said METH2 polypeptides is highly variant because the genus encompasses members having numerous structural alterations from SEQ ID NO:4, and members which minimally comprising portions of SEQ ID NO:4. Neither the claims nor the specification provide a definition for "METH2" which would limit the members of this genus to proteins having a specific functional activity. Thus, the disclosure of SEQ ID NO:4 does not adequately describe the proteins encompassed by the genus of METH2 because the genus encompasses molecules which have widely different functional and structural attributes from SEQ ID NO:4. One of kill in the art Further, a method claim reliant upon the identity of a genus of METH2 cannot itself be adequately described if the products on which the claim are reliant are not themselves adequately described.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1 and 5 are rejected under 35 U.S.C. 102(b) as being anticipated by Bouck et al (WO 93/16716) as evidenced by Vazquez et al (FASEB Journal, 1997, Vol. 11, abstract# 1947).

Claims 1 and 5 are drawn in part to a method of in treating an individual comprising administering an effective amount of METH2, wherein said method is used to treat vasculogenesis.

Bouck et al disclose a method of treating vasculogenesis comprising the administration of certain peptides derived from of thrombospondin (claim 14). The specification states that METH2 polypeptides may contain up to 50 conservative or non-conservative amino acid substitutions and that the substitutions may be made in full-length or any other METH2 variant, including N and/or C-terminal deletion mutants, METH2 polypeptides lacking one or more domains or hybrid METH2 molecules (page 205, lines 11-4 and lines 22-26). Thus, the polypeptides containing the amino acid substitutions can read on a fragment of METH2 lacking all the domains with the exception of a thrombospondin domain. Further, Vazquez et al disclose that METH2 has the anti-angiogenesis domains of thrombospondin-1 as taught by Bouck et al. Because Bouck et al disclose the administration of a thrombospondin derived peptide fragment, the specific embodiments of the claims are met. The thrombospondin fragment of Bouck et al is thus a METH2 polypeptide because it is a fragment of METH2 comprising 1-50 conservative or non-conservative amino acid substitutions.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later

invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-3 and 5-7 are rejected under 35 U.S.C. 103(a) as being unpatentable over O'Reilly et al (U.S. 5,639,725) in view of Bouck et al (WO 93/16716).
O'Reilly et al teach a method for treating an individual suffering from benign tumors, for example hemangiomas, acoustic neuromas, neurofibromas, trachomas, and pyogenic granulomas; rheumatoid arthritis; psoriasis; ocular angiogenic diseases, for example, diabetic retinopathy, retinopathy of prematurity, macular degeneration, corneal graft rejection, neovascular glaucoma, retrolental fibroplasia, rubeosis; Osler-Webber Syndrome; myocardial angiogenesis; plaque neovascularization; telangiectasia; hemophiliac joints; angiofibroma; and wound granulation, intestinal adhesions, atherosclerosis, scleroderma, and hypertrophic scars, i.e., keloids (column 10, lines 6-25). O'Reilly et al teach that angiostatin can be used as a birth control agent by preventing vascularization required for embryo implantation (column 10, lines 25-27). O'Reilly et al do not teach the administration of METH2 polypeptides, or the treatment of the aforementioned diseases further comprising administering another anti-angiogenic compound.

Bouck et al teach a method of treating vasculogenesis comprising the administration of certain peptides derived from of thrombospondin (claim 14). The specification states that METH2 polypeptides may contain up to 50 conservative or non-conservative amino acid substitutions and that the substitutions may be made in full-length or any other METH2 variant, including N and/or C-terminal deletion mutants, METH2 polypeptides lacking one or more domains or hybrid METH2 molecules (page 205, lines 11-4 and lines 22-26). Thus, the polypeptides containing the amino acid substitutions can read on a fragment of METH2 lacking all the domains with the exception of a thrombospondin domain. Because Bouck et al teach the administration of a thrombospondin derived peptide fragment, the specific embodiments of the claims with respect to the METH2 polypeptide are met. The thrombospondin fragment of Bouck et al is thus a METH2 polypeptide because it is a fragment of METH2 comprising 1-50 conservative or non-conservative amino acid substitutions.

It would have been prima facie obvious at the time the claimed invention was made to combine the administration of the peptide fragments taught by Bouck et al in the method of

treatment taught by O'Reilly et al. One of skill in the art would have been motivated to do so because both products are taught to exert a similar therapeutic effect. The instant situation is amenable to the type of analysis set forth in *In re Kerkhoven*, 205 USPQ 1069 (CCPA 1980) wherein the court held that it is *prima facie* obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose in order to produce a third composition that is to be used for the very same purpose since the idea of combining them flows logically from their having been taught individually in the prior art. Applying the same logic to the instant method claims, given the teaching of the prior art of methods of using angiostatin and fragments of thrombospondin as anti-angiogenic agents, it would have been obvious to use both the angiostatin and the fragments of thrombospondin for the treatment of benign tumors, for example hemangiomas, acoustic neuromas, neurofibromas, trachomas, and pyogenic granulomas; rheumatoid arthritis; psoriasis; ocular angiogenic diseases, for example, diabetic retinopathy, retinopathy of prematurity, macular degeneration, corneal graft rejection, neovascular glaucoma, retrolental fibroplasia, rubeosis; Osler-Webber Syndrome; myocardial angiogenesis; plaque neovascularization; telangiectasia; hemophiliac joints; angiofibroma; and wound granulation, intestinal adhesions, atherosclerosis, scleroderma, and hypertrophic scars, and for preventing placental implantation because the idea of doing so would have logically followed from having been individually taught in the prior art to be useful as anti-angiogenic agents.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Karen A Canella whose telephone number is (571)272-0828. The examiner can normally be reached on 10 a.m. to 9 p.m. M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (571)272-0841. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Karen A. Canella, Ph.D.
05/16/2004

KAREN A. CANELLA PH.D
PRIMARY EXAMINER